The amendments to the specification correct minor typographical errors noted by the Examiner.

The amendments to claim 1 add a method step, as requested by the Examiner, and incorporates into claim 1 a recitation that the disorders encompassed by the claims are disorders of the cytochrome P450 metabolic pathway for unsaturated fatty acids. The amendment is supported throughout the specification, including page 19, lines 1-3, and page 18, lines 26-28.

III. The Office Action

The Action imposes certain objections and rejects claims 1-10 on several grounds. Applicants amend in part and traverse all the rejections. For the Examiner's convenience, the rejections are discussed below in the order in which they are presented in the Action.

A. Objection to the Declaration

The Action alleges that the oath or declaration is defective. The Action alleges that non-initialed or non-dated alterations have been made to the oath in that "[t]he first page of the declaration states the citizenship of Jiang Zheng as China but the citizenship changed to the United States on the second page of the declaration." Action, at page 2, paragraph numbered "1".

The Action is in error. What MPEP §602.01 (8th Ed., Feb 2003 revision)[1] prohibits is any alteration or change in the wording of the declaration after it has been signed. The subject inventors' declaration contains no alterations or changes after it was signed. The declarations submitted with respect to this application include a complete declaration by inventors Hammock, Zurek, Newman, and Gee, which is signed and dated by each inventor. There is also a separate declaration, with a different indication of citizenship for inventor Jiang Zheng, that is dated or signed by inventor Jiang Zheng.

---

[1] All citations to the MPEP herein are to the 8th edition, February 2003 revision.

There is therefore no wording on either declaration which has been amended, altered or changed after it was signed by the inventors.

As noted, what the Action confuses for an undated and unsigned change is the difference in the indication of citizenship for inventor Jiang Zheng. That citizenship information was printed on each copy of the declaration and was clearly there as of the date of signature by the inventors. It is therefore not an amendment, alteration or change in the wording after it has been signed. Applicants respectfully note that in each declaration, the inventors signing that declaration believe that they are the first and true inventors, and states the citizenship of the inventors signing that declaration. The declarations therefore comply with 35 U.S.C. § 115 as set forth at §602 of the MPEP (at page 600-26). There is no requirement in the statute, or in the MPEP, that each inventor also make a declaration as to the citizenship of the other inventors, which in any event may be unknown to them.

The Action's position would require re-execution of declarations wherever there was a difference between one page of a declaration signed and dated by one inventor, and a second declaration signed and dated by another. For example, a correction of his or her address by a single inventor on a separate page would trigger the need for re-executed declarations by every other inventor, even though there was no unsigned or undated change or alteration on the declaration the other inventors had already signed and dated. Applicants submit that the Action's position is not mandated by the patent statue, the PTO's regulations, or by the MPEP. The objection should be reconsidered and, upon reconsideration, withdrawn.

B. Objection to Informalities

The Action objects to the disclosure for minor typographical errors. Action, at pages 2-3. The errors have been corrected by the amendments herein. The amendments obviate the objection.

C. Rejection Under 35 U.S.C. § 112, 2nd Paragraph

The Action rejects claims 1-10 under 35 U.S.C. §112, 2nd paragraph, as allegedly indefinite. According to the Action, claims 1-10 are drawn to a method of identifying a patient with a disorder or at risk of developing a disorder, but do not specify steps. Action, at page 3. The Action alleges that the claims specify that the method is an immunoassay, that "there are a myriad of immunoassays available. Thus, without specified steps, [the claims] are vague and indefinite." *Id.* Applicants amend in part and traverse in part.

Claim 1 has been amended to recite that the method comprises assaying the levels of diols or glucuronide conjugates in the sample, and determining whether those levels are increased, wherein an increased level is indicative of a patient who has or who is at risk for developing a disorder of cytochrome P450 metabolism of unsaturated fatty acids. The amendments to the claims therefore add a method step and tie the result of the method to the preamble. Applicants respectfully submit that, as amended, claim 1 is now free of the Action's concerns regarding indefiniteness. Reconsideration, and withdrawal, of the rejection are therefore respectfully requested.

While the above is sufficient to respond to the rejection, for the sake of good order, Applicants also point out that the Action seems to assume that the methods of the invention are necessarily immunoassays. It is true that immunoassays are a particularly convenient method for assaying for levels of linoleic acid diols or glucuronide conjugates in a sample, and such assays are specifically claimed in dependent claims 5-8. Claim 1, however, is not limited to immunoassays: any assay that can measure levels of the diols or glucuronide conjugates can be used to assay the levels.

For example, the specification notes that "[s]everal spectral based assays exist based on the reactivity or tendency of the resulting diol product to hydrogen bond (see, e.g., Wixstrom, and Hammock, *Anal. Biochem*, 174:291-299 (1985) and Dietz, et al., *Anal. Biochem.* 216:176-187 (1994))." Specification, at page 25, line 34, to page 26, line 3. The cited publications are incorporated into the specification by reference (see,

page 42, lines 15-17) and therefore legally are and always have been part of the specification's teachings.

Other analytical techniques to determine the levels of diols or glucuronide conjugates in a sample were also well known in the art prior to the priority date of the application. For example, Jude et al., Arch Biochem Biophy 380(2):294-302 (2000) (hereafter, "Jude"), a reference predating the priority date of the application and cited by the Action *against* the application in connection with another rejection, shows that diols could be detected using high pressure liquid chromatography ("HPLC," Jude, at page 296, left column) and gas chromatography mass spectroscopy (*id.* at page 296, right column), while glucuronides were analyzed using thin layer chromatography and HPLC-mass spectroscopy (*id.*, at page 296, right column, to page 297, left column). Similarly, Street et al., J Biol Chem 271:3507-3516 (1996) (hereafter "Street"), another reference which predates the priority date of the application and which is cited by the Action *against* the application, shows the use fast atom bombardment-mass spectroscopy ("FAB-MS") to detect the presence of glucuronic acid conjugates of fatty acids. *See*, Street at page 3514, right column.

Since these, and other assays, were well known in the art prior to the present specification, they would be well known to practitioners and did not need to be set forth in the specification. As noted by the MPEP, there is an inverse correlation between what is known by persons of skill in the art and what needs to be set out in the specification. In this regard, § 2163 of the MPEP states, at page 2100-164, right column, that information which is well known to persons of skill in the art need not be set forth in the specification. Applicants respectfully note that the actual legal standard articulated by the U.S. Court of Appeals for the Federal Circuit in the case cited by the MPEP is even stronger: the Court held that the specification need not state, "and preferably omits," that which is well known to persons of skill in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986). The specification therefore did not need to set forth all of the various assays known to persons of skill in the art to enable their use in the claimed methods.

Accordingly, for all the reasons set forth above, Applicants submit that claim 1 as amended, and the claims dependent thereon, obviate the rejection under § 112. Applicants respectfully request that the rejection be reconsidered and, upon reconsideration, be withdrawn.

D. Rejection Of the Claims As Obvious

1. Statement of the Rejection and General Response Thereto

Claims 1-10 are rejected by as obvious under 35 U.S.C. §103(a) over Bursten, U.S. Patent 5,780,237 (hereafter "Bursten") in view of Jude and further in view of Street. According to the Action, Bursten discloses a "diagnostic assay for ARDS by measuring levels of unsaturated fatty acids in a body fluid" (Action, at page 4), and that Bursten's teachings differ from the present claims in that

> Bursten's method assays linoleic acid whereas Applicant assays for linoleic acid diol or its respective glucuronide conjugate. However, Jude et al. and Street et al. teach that linoleic acid diol glucuronides and leukotoxin diol have been isolated from urine of patients suffering from generalized peroxisomal disorders . . ..

Applicants amend in part and traverse.

The Action's contention is that linoleic acid diols and glucuronides have been isolated from urine of patients suffering from generalized peroxisomal disorders. As stated in the MPEP, "[t]o establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP §2143.03. The references do not teach or suggest all of the claim limitations of claim 1 as amended.

Claim 1 has been amended to recite that increased levels of the diols and glucuronides can be used to determine whether a person has or is at risk for a disorder of cytochrome P450 unsaturated fatty acid metabolism. The generalized peroxisomal disorders considered by Street and by Jude are rare, congenital disorders, most of which

are fatal in infancy, adolescence or early adulthood. These disorders are due to the absence or dysfunction of one or more peroxisome enzymes. For the Examiner's convenience, Applicants have included as Exhibit 1 to this Amendment a printout of information on peroxisomal disorders from an internet health information site.

As noted in the Background of the specification, the cytochrome P450 ("CYP") monooxygenase pathway metabolizes unsaturated fatty acids (FAs) by forming epoxy lipids (and, in other pathways, alcohols). These lipids are then hydrolyzed by epoxide hydrolase (EH) to form dihydroxy forms that can then be used to form glucuronides. See, specification, at page 1, lines 27-33. As is well known in the art, however, peroxisomes function to perform β-oxidation of FAs and to detoxify H_2O_2. If the enzymes of a peroxisome malfunction or are not present, therefore, it would be expected that there would be an excess present in the peroxisome of H_2O_2 and a consequent excess of FA epoxides, which would then be available to be hydrolyzed into larger than normal amounts of diols or glucuronids.

While peroxisome disorders might be expected, therefore to result in more than the normal amount of diols or glucuronides, the references cited provide no reason one of skill would expect to detect increased levels of FA diols or glucuronides from abnormal cytochrome P450 metabolism. Cytochrome P450 metabolism employs enzymes, rather than H_2O_2, to oxidize FAs into epoxides. Therefore, the teachings of Jude and Street do not teach or suggest claim 1 as amended.

Claim 1 has been amended to add a recitation that a determination be made as to whether the levels of linoleic acid diols or glucuronide conjugates has been increased. Bursten by itself does not teach or suggest measuring the level of linoleic acid diols or glucuronide conjugates. Therefore, Bursten must be combined with Street or with Jude, or both, to supply the claim element of determining whether or not the stated diols or glucuronides have increased. The rejection combines Street with Bursten because Street "teaches that measurement of these compounds could be useful in the diagnosis of peroxisomal disorders (a group of lipid metabolic disorders)." Action, at page 5. Claim 1, however, now recites the diagnosis of disorders of the P450 cytochrome

unsaturated fatty acid metabolism. Since peroxisomes, if they use the cytochrome P450 metabolic pathway at all, do not do so to a significant degree, the Action's argument no longer supplies a motivation to combine Street with Bursten.

Similarly, Jude is cited by the Action only as teaching that linoleic acid diols, glucuronides and leukotoxin have been isolated from urine of children with generalized peroxisomal disorders. Action, at page 5. Claim 1, however, now recites the diagnosis of disorders of the P450 cytochrome unsaturated fatty acid metabolism. Since peroxisomes, if they use the cytochrome P450 metabolic pathway at all, do not do so to a significant degree, the Action's argument no longer supplies a motivation to combine Jude with Bursten.

Accordingly, Applicants submit that claim 1 as amended, and the claims dependent on claim 1, are not obvious over Bursten by itself or in view of Street or Jude, or both. Reconsideration, and withdrawal, of the rejection are respectfully requested.

2. Rejection as applied to Claim 4

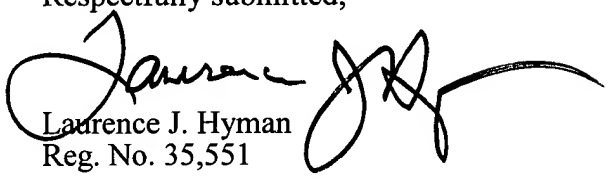
As set forth in the preceding section, claim 1 as amended and the claims dependent thereon are not obvious over Bursten, Street and Jude. For the sake of good order, Applicants note that the rejection is not in any event properly applied to claim 4. The Action concedes, at page 2, under "Status of the Application," that a "search of available literature has not yielded any evidence to support the linkage [of] linoleic acid diols to pre-eclampsia, eclampsia or pregnancy-related hypertension." Therefore, the Action provides no reference over which claim 4, which recites diagnosing a person at risk for these conditions by assaying increased levels of such a diol or glucuronide, can be found to be obvious. The rejection of this claim as obvious over Bursten, Jude and Street therefore should be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Enclosures: Pages on peroxisomal disorders

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Page 2, lines 3-20:

The leukotoxin pathway appears to be involved in regulation of vascular permeability, and failure to regulate vascular permeability is associated with a variety of vascular diseases including adult respiratory distress syndrome (ARDS). ARDS is a pulmonary disease that has a mortality rate of 50% and results from lung lesions that are caused by a variety of conditions found in trauma patients and in severe burn victims. (Ingram, R.H. Jr., *Harrison's Principals of Internal Medicine*, 13:1240 (1995)). In ARDS there is an acute inflammatory reaction with high numbers of neutrophils that migrate into the interstitium and alveoli. If this progresses there is increased inflammation, edema, cell proliferation, and the end result is impaired ability to extract oxygen. The exact cause of ARDS is not known. However it has been hypothesized that over-activation of neutrophils leads to the release of linoleic acid in high levels via phospholipase A_2 activity. Linoleic acid in turn is converted to 9,10-epoxy-12-octadecenoate enzymatically by neutrophil cytochrome P-450 epoxygenase and/or a burst of active oxygen. This lipid epoxide, or leukotoxin, is found in high levels in burned skin and in the serum and bronchial lavage of burn patients. Furthermore, when injected into rats, mice, dogs, and other mammals it causes ARDS. With the possible exception of glucocorticoids, there have not been therapeutic agents known to be effective in preventing or ameliorating the tissue injury, such as microvascular damage, associated with acute inflammation that occurs during the early development of ARDS.

Page 2, lines 21-31

Hypertension is the most common risk factor for cardiovascular disease, the leading cause of death in many developed countries. Essential hypertension, the most common form of hypertension, is usually defined as high blood pressure in which

secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes are not present (for a discussion of the definition and etiology of essential hypertension *see*, Carretero and Oparil *Circulation* 101:329-335 (2000) and Carretero, O.A. and S. Oparil. *Circulation* 101:446-453 (2000)). Hypertension can also lead to potentially severe complications in human gestation. Pre-eclampsia, eclampsia and pregnancy-induced hypertension (PIH) are characterized by elevated blood pressure, proteinuria and edema. Pregnancy induced hypertension is very common in first pregnancies. Although progression to full eclampsia is rare, morbidity and mortality are very high from this disorder.

Page 25, lines 16-26:

Any of a number of standard assays for determining epoxide hydrolase activity can be used. For example, suitable assays are described in Gill, *et al.*, *Anal Biochem* **131**, 273-282 (1983); and Borhan, *et al.*, *Analytical Biochemistry* **231**, 188-200 (1995)[)]. Suitable *in vitro* assays are described in Zeldin *et al. J Biol. Chem.* 268:6402-6407 (1993). Suitable *in vivo* assays are described in Zeldin *et al. Arch Biochem Biophys* 330:87-96 (1996). Assays for epoxide hydrolase using both putative natural substrates and surrogate substrates have been reviewed (*see*, Hammock, *et al. In: Methods in Enzymology, Volume III, Steroids and Isoprenoids, Part B*, (Law, J.H. and H.C. Rilling, eds. 1985), Academic Press, Orlando, Florida, pp. 303-311 and Wixtrom *et al.* , *In: Biochemical Pharmacology and Toxicology, Vol. 1: Methodological Aspects of Drug Metabolizing Enzymes*, (Zakim, D. and D.A. Vessey, eds. 1985), John Wiley & Sons, Inc., New York, pp. 1-93).

Page 30, line 27, to page 31, line 4:

Generally, to assure specific hybridization, the antisense sequence is substantially complementary to the target sequence. In certain embodiments, the antisense sequence is exactly complementary to the target sequence. The antisense polynucleotides may also include, however, nucleotide substitutions, additions, deletions,

transitions, transpositions, or modifications, or other nucleic acid sequences or non-nucleic acid moieties so long as specific binding to the relevant target sequence corresponding to the EH gene is retained as a functional property of the polynucleotide. As one embodiment of the antisense molecules form a triple helix-containing, or "triplex" nucleic acid. Triple helix formation results in inhibition of gene expression by, for example, preventing transcription of the target gene (*see*, *e.g.*, Cheng *et al.*, 1988, *J. Biol. Chem.* 263:15110; Ferrin and Camerini-Otero, 1991, *Science* 354:1494; Ramdas *et al.*, 1989, *J. Biol. Chem.* 264:17395; Strobel *et al.*, 1991, *Science* 254:1639; and Rigas *et al.*, 1986, *Proc. Natl. Acad. Sci. U.S.A.* 83:9591).SF 1453494 v1

IN THE CLAIMS:

12. (Amended) A method of identifying a patient with a disorder or at risk for a disorder with abnormal regulation of cytochrome P450 metabolism of unsaturated fatty acids [metabolism], the method comprising

(a) assaying levels of a linoleic acid diol or its respective glucuronide conjugate in a sample from the patient, and

(b) determining whether said levels are increased,

wherein increased levels in the sample indicate the patient has, or is at risk for, a disorder with abnormal regulation of cytochrome P450 metabolism of unsaturated fatty acids.

Encyclopedia Index P

Peroxisomal disorders

Definition

Peroxisomal disorders are a group of congenital diseases characterized by the absence of normal peroxisomes in the cells of the body. Peroxisomes are organelles within a cell that contain enzymes responsible for critical cellular processes, including oxidation of fatty acids, biosynthesis of membrane phospholipids (plasmalogens), cholesterol, and bile acids, conversion of amino acids into glucose, reduction of hydrogen peroxide by catalase, and prevention of excess synthesis of oxalate (which can form crystals with calcium, resulting in **kidney stones**). Peroxisomal disorders are subdivided into two major categories: those disorders resulting from a failure to form intact, normal peroxisomes, resulting in multiple metabolical abnormalities, which are referred to as peroxisome biogenesis disorders (PBD) or as generalized peroxisomal disorders; and those disorders resulting from the deficiency of a single peroxisomal enzyme. There are about 25 peroxisomal disorders known, although the number of diseases that are considered to be separate, distinct peroxisomal disorders varies among researchers and health care practitioners.

Description

A cell can contain several hundred peroxisomes, which are round or oval bodies with diameters of about 0.5 micron, that contain proteins that function as enzymes in metabolic processes. By definition, a peroxisome must contain catalase, which is an enzyme that breaks down hydrogen peroxide.

Approximately fifty different biochemical reactions occur entirely or partially within a peroxisome. Some of the processes are anabolic, or constructive, resulting in the

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synthesis of essential biochemical compounds, including bile acids, cholesterol, plasmalogens, and docosahexanoic acid (DHA), which is a long chain fatty acid that is a component of complex lipids, including the membranes of the central nervous system. Other reactions are catabolic, or destructive, and lead to the destruction of some fatty acids, including very long chain fatty acids (VLCFAs, fatty acids with more than 22 carbon atoms in their chains), phytanic acid, pipecolic acid, and the prostoglandins.The peroxisome is involved in breaking down VLCFAs to lengths that the body can use or get rid of.

When VLCFAs accumulate due to abnormal functioning of the peroxisomes, they are disruptive to the structure and stability of certain cells, especially those associated with the central nervous system and the myelin sheath, which is the fatty covering of nerve fibers. The peroxisomal disorders that include effects on the growth of the myelin sheath are considered to be part of a group of genetic disorders referred to as leukodystrophies.

There are many other metabolic deficiencies that can occur in those who have peroxisomal disorders, which result in other types of detrimental effects, and together result in the abnormalities associated with the peroxisomal disorders. Unfortunately, it is not known how these abnormalities, and combinations of abnormalities, cause the disabilities seen in those afflicted with the disease.

Peroxisomal disorders form a heterogeneous disease group, with different degrees of severity. Included in the group referred to as PBD are:

- Zellweger syndrome (ZS), which is usually fatal within the first year of life,
- neonatal **adrenoleukodystrophy** (NALD), which is usually fatal within the first ten years,
- infantile Refsum disease (IRD), which is not as devastating as ZS and NALD, as the children with this disorder with time and patience can develop some degree of motor, cognitive, and communication skills, although **death** generally occurs during the second decade of life.

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- Life Clock

- rhizomelic chondrodysplasia punctata (RCDP), which in its most severe form is fatal within the first year or two of life; however, survival into the teens has been known to occur. It is characterized by shortening of the proximal limbs (i.e., the legs from knee to foot, and the arms from elbow to hand) and,

- Zellweger-like syndrome, which is fatal in infancy, and is known to be a defect of three particular enzymes.

The differences among these disorders are continuous, with overlap between abnormalities. The range of disease abnormalities may be a result of a corresponding range of peroxisome failure; that is, in severe cases of ZS, the failure is nearly complete, while in IRD, there is some degree of peroxisome activity.

In peroxisomal single-enzyme disorders, the peroxisome is intact and functioning, but there is a defect in only one enzymatic process, with only one corresponding biochemical abnormality. However, these disorders can be as severe as those in which peroxisomal activity is nearly or completely absent.

X-linked adrenoleukodystrophy (X-ALD) is the most common of the peroxisomal disorders, affecting about one in 20,000 males. It is estimated that there are about 1,400 people in the United States with the disorder. In X-ALD there is a deficiency in the enzyme that breaks down VLCFAs, which then accumulate in the myelin and adrenal glands. Onset of X-ALD-related neurological symptoms occurs at about five-12 years of age, with death occurring within one to 10 years after onset of symptoms. In addition to physical abnormalities seen in other types of peroxisomal disorders, common symptoms of X-ALD also include behavioral changes such as abnormal withdrawal or aggression, poor memory, **dementia**, and poor academic performance. Other symptoms are muscle weakness and difficulties with hearing, speech, and vision. As the disease progresses, muscle tone deteriorates, swallowing becomes difficult and the patient becomes comatose. Unless treated with a diet that include's Lorenzo's oil, the disease will result in **paralysis**, **hearing loss**, blindness, **vegetative state**, and death. There are also milder forms of X-ALD: an adult on-set ALD that typically begins

between the ages of 21 and 35, and a form that is occasionally seen in women who are carriers of the disorder. In addition to X-ALD, there are at least ten other single-enzyme peroxisomal disorders, each with its own specific abnormalities.

Causes and symptoms

Most peroxisomal disorders are inherited autosomal recessive diseases, with X-ALD as an exception. They occur in all countries, among all races and ethnic groups. They are extremely rare, with frequencies reported at one in 30,000 to one in 150,000, although these numbers are only estimates.

In general, developmental delay, **mental retardation**, and vision and hearing impairment are common in those who have these disorders. Acquisition of speech appears to be especially difficult, and because of the reduced communication abilities, **autism** is common in those who live longer. Peroxisomal disorder patients have decreased muscle tone (hypotonia), which in the most severe cases is generalized, while in less severe cases, is usually restricted to the neck and trunk muscles. Sometimes this lack of control is only noticeable by a curved back in the sitting position. Head control and independent sitting is delayed, with most patients unable to walk independently.

Failure to thrive is a common characteristic of patients peroxisomal disorder, along with an enlarged liver, abnormalities in liver enzyme function, and loss of fats in stools (steatorrhea).

Peroxisomal disorders are also associated with facial abnormalities, including high forehead, frontal bossing (swelling), small face, low set ears, and slanted eyes. These characteristics may not be prominent in some children, and are especially difficult to identify in an infant.

Diagnosis

Since hearing and vision deficiencies may be difficult to identify in infants, peroxisomal disorders are usually detected by observations of failure to thrive, hypotonia, mental retardation, widely open fontanel, abnormalities in liver enzymes, and an enlarged liver. If peroxisomal disorders are suspected, blood plasma assays for VLCFAs,

phytanic acid, and pipecolic acid are conducted. Additional tests include plasmalogen biosynthesis potential.

Treatment

For many of the peroxisomal disorders, there is no standard course of treatment, with supportive treatment strategies focusing on alleviation of complications and symptoms. In general, most treatments that are attempted are dietary, whereby attempts are made to artificially correct biochemical abnormalities associated with the disorders. Therapies include supplementation of the diet with antioxidant **vitamins**, or limitation of intake of fatty acids, especially VLCFAs.

Another area of dietary therapy that is being investigated is the supplementation of the diet with pure DHA, given as early in life as possible, in conjunction with a normal well-balanced diet. Some results have indicated that if given soon enough during development, DHA therapy may prevent some of the devastating consequences of peroxisomal disorders, including the loss of vision and brain damage.

Other treatment strategies include addition of important missing chemicals. For example, in disorders where there is faulty adrenal function, replacement adrenal hormone therapy is used.

Any dietary changes should be monitored biochemically to determine if the supplements are having their desired effects and are not causing additional adverse effects.

A treatment for a specific type of peroxisomal disorder includes bone marrow transplants for X-ALD, which may be effective if used early in the course of the childhood form of the disease.

Physical and psychological therapies are important for all types of peroxisomal disorders.

Alternative treatment

Patients with peroxisomal disorders, and particularly X-ALD, have been treated with a mixture of glycerol trioleate-glycerol trieucate (4:1 by volume), prepared from olive and rapeseed oils, and referred to as Lorenzo's oil (developed by parents of a son,

Lorenzo, who had X-ALD, whose story was documented in the 1992 movie, *Lorenzo's Oil*), to decrease the levels of VLCFA. Other **diets** that have been tried include dietary supplementation with plasmalogen precursors to increase plasmalogen levels and with cholic acid to normalize bile acids. However, there has been only little success demonstrated with the use of these treatments. More research is needed to determine the long-term safety and effectiveness of these treatment strategies.

Prognosis

Peroxisomal disorders range from life-threatening to cases in which people may function with some degree of mental and motor retardation. As of 2001, there is not yet a cure. Enzyme replacement therapies, including enzyme infusion, transplantation, and **gene therapy**, may hold promise for future advances in the treatment of these disorders. Research is being conducted to increase scientific understanding of these disorders and to find ways to prevent, treat, and cure them.

Prevention

Unfortunately not enough is yet known about these diseases to develop comprehensive strategies for prevention. **Genetic counseling** is recommended for known or suspected carriers. As genes are identified that result in the disorders, **genetic testing** is being developed to identify carriers, who then can manage their reproduction to avoid the possibility of children being born with these deficiencies. As the genetic bases for the disorders is defined, prenatal diagnosis and identification of carriers will be facilitated. For example, for X-ALD, diagnosis can be made from cultured skin fibroblasts or amniotic fluid cells. This allows prenatal diagnosis and carrier identification in 90% of those affected. More recently it has been shown that biochemical diagnosis can be performed through chorionic villi biopsy, a procedure performed very early in the first trimester of **pregnancy**.

Animal models of ZS and X-ADL have been developed and are providing researchers with methods to define pathogenic mechanisms and to evaluate new therapies.

Key Terms

Autosome
A chromosome not involved in sex determination.

Autosomal recessive inheritance
Two copies of an altered gene located on one of the autosomes must be present for an individual to be affected with the trait or condition determined by that gene:

Fontanel
One of the membranous intervals between the uncompleted angles of the parietal and neighboring bones of a fetal or young skull; so called because it exhibits a rhythmical pulsation.

Organelle
Specialized structure within a cell, which is separated from the rest of the cell by a membrane composed of lipids and proteins, where chemical and metabolic functions take place.

For Your Information

Books

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Periodicals

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Organizations

- National Institute of Neurological Disorders and Stroke, NIH Neurological Institute. P.O. Box 5801 Bethesda, MD 20824. (800) 352-9424. http://www.ninds.nih.gov/index.htm
- National Organization for Rare Disorders P.O. Box 8923, New Fairfield, CT 06812- 8923 http

Other

- The Peroxisome Website. http://www.peroxisome.org.

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